Heart Failure with Preserved Ejection Fraction

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KEYWORDS

- Heart failure with preserved ejection fraction • Diastolic dysfunction
- Diagnostic uncertainty • Comorbidities • Guideline-directed medical therapy

KEY POINTS

- Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome where patients exhibit an ejection fraction (EF) ≥50%, cardiac dysfunction, and pulmonary or systemic congestion.
- Standard cardiac-specific evaluation for HFpEF should include assessment for noncardiac causes of dyspnea; if the diagnosis remains unclear, diagnostic algorithms and/or advanced cardiac testing may be utilized.
- Therapeutic management of patients with HFpEF is directed at the optimization of comorbidities, including hypertension, coronary artery disease, atrial fibrillation, chronic kidney disease, obesity, chronic obstructive pulmonary disease, and diabetes mellitus.
- HFpEF management includes loop diuretics in individuals with fluid retention, sodium-glucose cotransporter-2 inhibitors, angiotensin receptor-neprilysin inhibitors, and mineralocorticoid-receptor antagonist therapies based on gender and EF specifications.
- Future directions for HFpEF include remote pulmonary artery pressure monitoring, splanchnic denervation, cardiac contractility monitoring, and interventions to address frailty and sarcopenia.

INTRODUCTION

Heart failure is a complex clinical syndrome characterized by structural or functional impairment of ventricular filling or ejection of blood, affecting more than 6 million Americans with a prevalence that is on the rise.[1] Current definitions distinguish heart failure types based on differences in left ventricular ejection fraction (LVEF). Heart failure with reduced ejection fraction (HFrEF) is marked by an LVEF less than 40%, heart failure with mildly reduced ejection fraction (HFmrEF) with LVEF of 41% to 50%, and heart failure with preserved ejection fraction (HFpEF) with LVEF ≥50%.[2–4] Approximately

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Med Clin N Am 109 (2025) 1175–1195
https://doi.org/10.1016/j.mcna.2025.04.006
0025-7125/25/Published by Elsevier Inc.
medical.theclinics.com

Abbreviations	
ACEi	ACE inhibitors
AF	atrial fibrillation
ARB	angiotensin-blocker
ARNI	angiotensin receptor-neprilysin inhibitor
BNP	brain natriuretic peptide
CAD	coronary artery disease
CCM	cardiac contractility modulation
CKD	chronic kidney disease
DM	diabetes mellitus
EF	ejection fraction
GDMT	guideline-directed medical therapy
GLP-1	glucagon-like peptide-1
HFA-PEFF	Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology
HFimpEF	heart failure with improved ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HTN	hypertension
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrial
LV	left ventricular
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid-receptor antagonist
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PCWP	pulmonary capillary wedge pressure
PLR	passive leg raise
SGLT2i	SGLT2 inhibitors
TR	tricuspid regurgitation

50% of patients with heart failure have preserved ejection fraction (EF),[5] in which symptoms and signs of heart failure exist in the setting of a (near) normal EF.[3]

The cardinal feature of HFpEF is evidence of increased left ventricular (LV) stiffness with impaired relaxation, which may be found by invasive (eg, right heart catheterization) or noninvasive modalities (eg, echocardiography) but more likely heralded by raised natriuretic peptides in the setting of either congestion and/or unexplained dyspnea.[4] It should be noted that natriuretic peptides may not be raised in approximately 20% of patients with HFpEF.[6] Prior to widespread adoption of the term HFpEF, "diastolic heart failure" was often used to denote this syndrome. This was extrapolated from the concept of "diastolic dysfunction," which describes the pathophysiology that may be encountered during the evaluation of this disorder. It is important to distinguish that this "dysfunction" refers to a mechanical abnormality of the heart rather than a clinical syndrome, and diastolic dysfunction often coexists in both HFrEF and HFpEF.[7] The substitution of this term for HFpEF is no longer recommended, as diagnosing this clinical syndrome can be challenging due to an incomplete understanding of its pathophysiology and overlapping features and outcomes with HFrEF.

The disease and economic burden of heart failure are astounding and characterized by a rising use of resources and costs due to increased procedures and complications of heart failure.[8] The 5-year mortality rates for people living with heart failure are 50% to 75%.[1] Patients with HFpEF are 1.4 times per year more likely to be hospitalized,[5] and the annual mortality for these patients is approximately 15%.[5,9] Compared with

HFrEF, the morbidity and mortality associated with HFpEF are similar.[4] In fact, there is no difference between HFpEF and HFrEF with regards to hospitalization and impact on quality of life.[7] Heart failure remains a leading cause of hospitalization among adults.[10,11] Heart failure-related hospitalizations make up nearly 50% direct costs in the care of patients with heart failure.[12] In 2020, the total costs for heart failure in the United States were estimated to be around $40 billion yearly and expected to increase to approximately $70 billion in 2030.[13] HFpEF accounts for a larger majority of total HF costs, in part due to the impact of comorbidities and high prevalence.[14]

Currently, there is a lack of robust evidence for some traditional guideline-directed medical therapies specifically targeted for HFpEF compared with those proven in HFrEF. Despite this, clinical practice guidelines for the management of HFpEF do exist and often emphasize relief of congestion and treatment of comorbidities in these patients.[3,4] Patients with HFpEF are typically older (>65 years) and more likely to be female than their counterparts with HFrEF.[15–17] More than 80% of patients with HFpEF are overweight or obese.[18,19] There is a higher prevalence of comorbid conditions including hypertension (HTN), diabetes, chronic kidney disease (CKD), atrial fibrillation (AF), and chronic obstructive pulmonary disease in people living with HFpEF.[20–24] Given the comparable outcomes in HFpEF with other types of heart failure, interventions should be implemented early to address current comorbid conditions and prevent additional morbidity and other poor outcomes for these patients. In this review, the diagnosis, treatment, and future directions in the management of HFpEF will be discussed.

DIAGNOSIS

Clinical Presentation

Patients with HFpEF classically present with dyspnea on exertion or at rest as well as fatigue. Some may concurrently present with overt signs of volume overload such as orthopnea, paroxysmal nocturnal dyspnea, bendopnea, pulmonary rales (ie, crackles), peripheral edema, or jugular venous distension, while many patients, as discussed later, may not have obvious evidence of congestion at rest.

Definition

Various definitions and classifications for heart failure have emerged over the years for diagnostic, research, and billing purposes, each having varying sensitivity and specificity based on the diagnostic parameters included. The most recent universal definition of heart failure published in the *Journal of Cardiac Failure* in 2021 defines heart failure as “a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion.”[2] HFpEF is a classification of heart failure delineated by an LVEF $\geq$50%.[3,4] As part of the clinical syndrome of heart failure, HFpEF is where patients have signs and symptoms of heart failure as a result of high LV filling pressure despite normal or near normal EF.[25–27] This phenomenon of high LV filling pressures manifests as abnormal diastolic filling, or diastolic dysfunction. Importantly, a patient must have signs and symptoms of heart failure to meet criteria for diagnosis; demonstration of diastolic dysfunction alone in the absence of signs and symptoms does not constitute the syndrome of heart failure.

Evaluation

Initial evaluation should include a comprehensive assessment for noncardiac causes of dyspnea on exertion such as restrictive and obstructive lung disease, obesity hypoventilation syndrome, and deconditioning, as well as metabolic causes such as anemia or primary liver or renal disease with decompensation. Multifactorial dyspnea is common, and many patients with confirmed HFpEF have concurrent conditions that may have explained their dyspnea such as AF, restrictive or obstructive pulmonary disease, anemia, and frailty. However, as HFpEF is a manageable distinct condition of increasing incidence that carries high morbidity and mortality, it remains important to evaluate patients extensively for this diagnosis while still considering alternative explanations for their dyspnea.[28,29]

Additionally, there are conditions that meet the HFpEF criteria with similar symptoms, evidence of congestion, and EF of at least 50%; however, with a different and treatable etiology. These conditions are often described as HFpEF “masqueraders” or “phenocopies” and include various conditions such as cardiac amyloidosis, cardiac sarcoidosis, hypertrophic cardiomyopathy, hemochromatosis, Fabry disease, myocarditis, high-output heart failure, pulmonary HTN, lung disease with cor pulmonale, congenital heart disease, valvular heart disease, and pericardial disease among others.[29]

Cardiac-specific work up should begin with the least invasive testing possible, including history, physical examination, chest radiograph, electrocardiogram, echocardiogram, and serum brain natriuretic peptides (BNPs) or N-terminal-BNP (NTProBNP).[30] As part of their 2019 guidelines for diagnosing HFpEF, the European Society of Cardiology recommends including laboratory testing for electrolytes including serum sodium and potassium, renal function, liver function, hemoglobin A1C, thyroid-stimulating hormone, a complete blood count, and an iron study panel.

Diastolic Dysfunction on Resting Transthoracic Echocardiogram

HFpEF is characterized by impaired relaxation resulting in stiffness of the left ventricle, ultimately culminating in increased filling pressures and left atrial (LA) dilation. Impaired relaxation is reflected on resting transthoracic echocardiogram (TTE) as slowed velocity of the return of the mitral annulus to its original position after systole. This velocity is termed e′. The increased LV pressures in diastole ultimately result in increased LA pressure, which, in advanced diastolic dysfunction, manifests as an increase in velocity of passive blood flow through the mitral valve. This velocity is visualized on TTE as the E wave. The ratio of E/e′ has been shown to correlate with left ventricular end-diastolic pressure (LVEDP), which is increased in HFpEF.[31] Thus, an E/e′ on resting TTE of greater than 14, septal e′ velocity less than 7 cm/s, or lateral e′ velocity less than 10 cm/s are consistent with diastolic dysfunction that may be present in HFpEF.[32] The American Society of Echocardiography and the European Association of Cardiovascular Imaging have recommended additional testing parameters to assess for diastolic dysfunction in patients with normal EF; these include measuring a tricuspid regurgitation (TR) velocity (maximum >2.8 m/s) and LA volume index (abnormal >34 mL/m^2). If more than half of these variables meet these criteria, this is considered consistent with diastolic dysfunction. If less than half meet the criteria, then diastolic function is considered normal. If exactly half meet the criteria, then this is inconclusive. Limitations to the accuracy of these measurements include mitral valve disease, heavy mitral calcification, arrhythmias (eg, AF), and hypertrophic cardiomyopathy, among others.[32]

If the patient is without overt evidence of congestion at rest or on preliminary testing and the diagnosis is not obvious, the patient should be then stratified for the risk of having HFpEF with the scoring systems later.

Diagnostic Score Algorithms

Two scoring systems exist for risk stratification, the first of which is the H2FPEF score validated in 2018.[33] Reddy and colleagues retrospectively evaluated patients who had been evaluated for noncardiac causes of dyspnea in the community and were referred for invasive hemodynamic testing. Parameters were identified that were highly predictive of HFpEF in those who tested positive on gold standard invasive testing in comparison to those who did not. Using this information, a scoring system was devised based on the presence of HTN requiring at least 2 antihypertensives, obesity, AF, pulmonary HTN, E/e′ greater than 9, and age greater than 60 to estimate a probability that a patient has HFpEF. The presence of persistent or paroxysmal AF yields 3 points, a BMI greater than 30 kg/m^2 yields 2 points, and all other variables yield 1 point. A H2FPEF score of $\geq$6 predicts a diagnosis of HFpEF with a probability $\geq$90%.

A second scoring system, HFA-PEFF (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology), proposed in 2019, entails a 3-step system in which a recommended preliminary work up is factored into the HFA-PEFF algorithm to generate a risk score.[30] The scoring system consists of major and minor criteria divided into functional, morphologic, and biomarker subcategories. A high-risk score of 5 or greater confirms the diagnosis of HFpEF, while a low score of 1 or less gives a low probability of a diagnosis of HFpEF. An intermediate score between 2 to 4 prompts further diagnostic evaluation with noninvasive stress testing versus invasive hemodynamic assessment $\pm$ stress testing. Initially, a tool proposed based on expert consensus, the HFA-PEFF algorithm has since been validated.[34] In a cohort of 270 patients being worked up for HFpEF from the Maastricht database, a score of at least 5 demonstrated a high specificity of 93% and PPV of 98%, whereas a low score of 0 to 1 had a sensitivity of 99% and an NPV of 73%.

Diagnostic Uncertainty

If the diagnosis remains inconclusive based on preliminary testing and the scoring systems above, the next step is to pursue exercise testing, as many patients may only demonstrate elevated intracardiac filling pressures during exercise.[31,35] This may be pursued noninvasively through stress TTE. Exercise testing in HFpEF demonstrates a blunted physiologic response of increased cardiac output and stroke volume to exercise, ultimately increasing filling pressures. This can be reflected on TTE as an increase in E/e′ correlating with increased LVEDP, often in conjunction with an increase in tricuspid regurgitation (TR) velocity at peak stress reflecting an increase in pulmonary artery systolic pressure (PASP).[36] An average E/e′ at peak stress of 15 or greater makes the diagnosis of HFpEF more likely both on its own and adds 2 points to the HFA-PEFF algorithm. A TR velocity of at least 3.4 m/s at peak stress in conjunction with an increased E/e′ adds an additional point to the HFA-PEFF algorithm but is not diagnostic on its own.[30]

If diagnosis remains inconclusive based on noninvasive exercise stress TTE, invasive cardiopulmonary exercise testing is recommended. This is usually done with a right heart catheterization to measure intracardiac pressures with subsequent measurements after supine exercise, usually performed with a stationary bicycle. Patients with HFpEF have been shown to have larger increases in pulmonary capillary wedge pressure (PCWP), LVEDP, and mean pulmonary artery (PA) pressure with exercise, as well as a blunted heart rate response, and a greater increase in PCWP in comparison to cardiac output, with a lower peak oxygen consumption.[35,37,38] Current European guidelines classify an invasive PCWP of at least 15 at rest or at least 25 mm Hg with exercise as diagnostic of HFpEF.[30]

Given that exercise testing may not be widely available, passive leg raise (PLR) can be used instead of exercise. In a study evaluating 109 patients who underwent both exercise and PLR hemodynamic testing, PCWP after PLR less than 11 mm Hg ruled out HFpEF with 100% sensitivity, and a PCWP after PLR of at least 19 mm Hg diagnosed HFpEF with 100% specificity.[39] Additionally, invasive hemodynamics after rapid volume expansion with saline has been studied as an alternative method of diagnosing HFpEF. In a study of 26 patients, 14 with HFpEF, rapid volume expansion did result in an increase in PCWP in patients with HFpEF, but to a lesser degree than with exercise (18$\pm$5 vs 10$\pm$4 mm Hg; $P<.0001$).[40] Using data from studies conducted to differentiate patients with pulmonary arterial hypertension (PAH) from those with PAH with occult HFpEF,[41,42] D'Alto and colleagues proposed an algorithm for the diagnosis of HFpEF using a saline challenge with the infusion of 7 mL/kg or 500 mL of saline within 5 to 10 minutes with measurement of PCWP at the end of the infusion with a PCWP of 18 mm Hg or higher being correlated with HFpEF.[43] However, further studies are needed to validate the use of saline challenge in diagnosis of HFpEF and exact parameter cutoffs, and exercise testing remains the gold standard and should be used when available. Patients who do not meet these parameters are classified as having noncardiac dyspnea. A diagnostic pathway for HFpEF is proposed in Fig. 1.

Underdiagnosis

Despite its increasing incidence and prevalence, HFpEF is still thought to be a relatively underdiagnosed condition.[35,44] This may in part be due to the inclusion of elevated natriuretic peptides in the definition of HFpEF, as they are often normal in

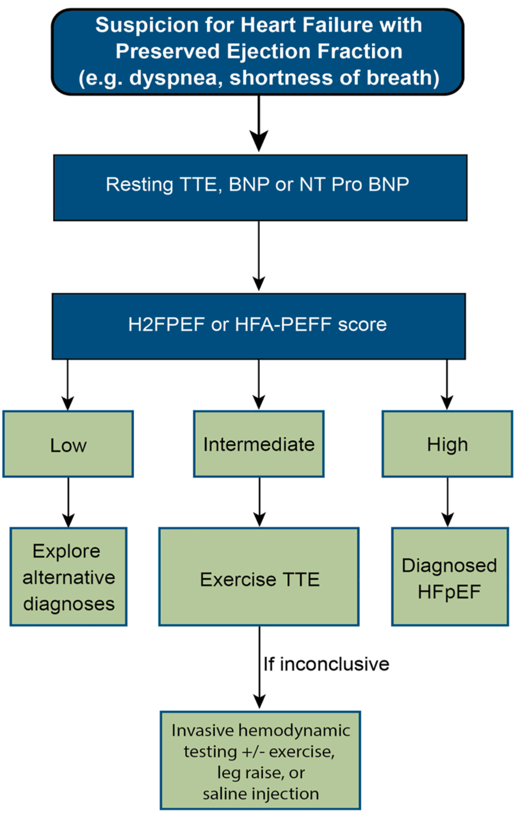

Fig. 1. Diagnostic pathway for heart failure with preserved ejection fraction.

about one-third of patients with HFpEF.[45] Multiple patient characteristics have been associated with falsely normal natriuretic peptide levels including obesity, African ancestry, insulin resistance, increased androgen states such as in men and postmenopausal women, presence of constrictive pericarditis, and even genetics.[46] The common diagnostic tool of transthoracic echocardiography has inherent limitations and may also underestimate intracardiac filling pressures in patients with obesity in part due to uncoupling between intravascular volume and pressures.[47] Physical examination signs of congestion such as jugular venous distension may also be more difficult to assess in patients with obesity. Additionally, some patients do not have elevated filling pressures on echocardiography at rest and require escalation to invasive cardiopulmonary exercise testing, which may not be readily available at most institutions, in order to reveal elevated intracardiac pressures that are diagnostic of HFpEF.[35]

TREATMENT

Caring for the patient with HFpEF involves management of systemic comorbidities as well as specific pharmacologic and nonpharmacologic therapies to target disease progression.

Management of Congestion

Signs and symptoms of volume overload are frequently found in patients with HFpEF and are directly correlated with functional intolerance as well as heart failure hospitalizations, cardiovascular death, and all-cause mortality.[48] Loop diuretics remain the preferred agents for management of congestion in heart failure patients.[49] The selection of loop diuretic and dose are largely dependent on the degree of congestion.[28] For patients unable to achieve sufficient decongestion with loop diuretics, additional agents including thiazides or mineralocorticoid-receptor antagonists (MRAs) can also be considered.[50]

Management of Comorbidities

The focus of therapeutic management strategies for patients with HFpEF is on optimization of both cardiovascular and noncardiovascular comorbidities (**Table 1**).[51] Multiple cardiac and noncardiac comorbidities including HTN, coronary artery disease (CAD), AF, CKD, obesity, COPD, and diabetes mellitus (DM) are shown to have a bidirectional association with HFpEF and an increased risk for morbidity and mortality associated with these comorbidities.[52]

HTN is one of the most common identified causes of HFpEF, with a prevalence of 60% to 89% in the HFpEF population.[51] Intensive control of systolic blood pressure in patients with HTN has been shown to consistently reduce the incidence of HF.[53] For patients with established HF, intensive blood pressure control may slow key pathways in disease progression.[54] Per guideline recommendations, adults with HFpEF should have blood pressure medications titrated to attain a systolic blood pressure less than 130 mm Hg.[55] The choice of antihypertensive therapy should be largely driven by comorbidities, cost, and tolerability. Beta-blocker use exclusively as antihypertensive agents should generally be avoided in patients with HFpEF due to concern for reduced tolerability given its negative chronotropic effects.[51] Indeed, the PRESERVE-HF trial demonstrated beta-blocker withdrawal significantly improved maximal functional capacity in HFpEF patients with chronotropic incompetence.[56] In addition to pharmacologic control, dietary sodium restriction has been shown to reduce blood pressure and is associated with favorable changes in ventricular diastolic function.[57]

Table 1
Management of comorbidities in heart failure with preserved ejection fraction

Medical Comorbidity	Management	Class of Recommendation
Hypertension	• Goal BP < 130/80 mm Hg • Diuretics, ARNI/ARB/MRA. Avoid beta blockers	Class I
Atrial fibrillation	• Consider early rhythm control $\pm$ catheter ablation • Anticoagulation based on CHA_2DS_2-VASc	Class IIa
Chronic kidney disease	• ACEi/ARB vs ARNI if eGFR $\geq$30 mL/min/1.73 m^2 • SGLT2i if eGFR $\geq$20 mL/min/1.73 m^2	Class IIa
Type 2 diabetes	• SGLT2i as first-line therapy • Metformin if eGFR $\geq$30 mL/min/1.73 m^2	Class IIa
Obesity	• Weight loss and lifestyle changes first-line • GLP-1 receptor antagonists growing in evidence	Class IIa
Coronary artery disease	• Testing and intervention guided by individual clinical presentation • Medical management per appropriate guidelines	No recommendation

CAD is present in greater than 50% of patients with HFpEF. CAD is associated with greater deterioration in systolic function and significantly worsened survival compared with patients without CAD.[58] Both epicardial coronary disease and increased coronary microvascular dysfunction are associated with worsening diastolic dysfunction and increased HFpEF hospitalizations.[59,60] Statins have been shown to be associated with reduced cardiovascular mortality and HF hospitalizations for patients with HFpEF.[61] Although there are no prospective trials to assess the impact of revascularization on symptoms, observational analysis suggests revascularization may be associated with preservation of cardiac function and improved outcomes in patients with HFpEF and CAD.[62] Notably, although nitrates are typically prescribed for relief of angina, the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) heart failure guidelines recommend against the routine use of nitrates to improve exercise capacity for patients with HFpEF and angina.[3] Additionally, the role of antiplatelet therapy in HFpEF remains unclear. Decisions regarding anticoagulation should be individualized based on patient comorbidities and bleeding risk.

AF and HFpEF commonly coexist and share many clinical features.[63] These comorbid conditions are associated with a higher risk for heart failure hospitalizations, likely reflecting heightened sensitivity to acute hemodynamic changes compared with patients with HFpEF in normal sinus rhythm.[64] Management strategies should aim to maintain normal sinus rhythm for these patients. Furthermore, catheter ablation remains a viable strategy in maintaining sinus rhythm, suggested to reduce heart failure hospitalization rates compared with medical therapy.[65] High-powered prospective trials are required to validate these findings. Furthermore, impaired diastolic function in HFpEF often results in low resting stroke volume and limited capacity to augment stroke volume during exertion. Consequently, aggressive rate control strategies may further compromise cardiac output and should be avoided.[51] Anticoagulation for patients with HFpEF and AF is based on their CHA_2DS_2-VASc score; however, given the high prevalence of HTN and older age in patients with HFpEF, anticoagulation in this patient population is uniformly indicated.[51]

CKD, as defined by an eGFR less than 60 mL/min/1.73 m^2, is found in up to 40% to 60% of patients with HFpEF, partially due to multiple common underlying comorbidities.[66] Management of CKD in HFpEF is largely guided by kidney disease guidelines; ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are both noted to reduce CKD progression in these patients.[49] Additionally, the PARAGON-HF trial noted less decline in renal function for HFpEF patients treated with angiotensin receptor-neprilysin inhibitor (ARNI) compared with ARB.[67] The EMPEROR-Preserved trial also noted less decline in renal function for HFpEF patients treated with empagliflozin compared with placebo.[68] As a result of these findings, sodium-glucose cotransporter-2 inhibitors (SGLT2i) are recommended over renin-angiotensin antagonists in controlling CKD.[51] A small decrement in eGFR may be encountered with use of these nephroprotective therapies.[51]

DM is present in roughly 45% of patients with HFpEF and is associated with increased morbidity and long-term mortality for these individuals.[69] Management strategies are limited. SGLT2i are strongly recommended given demonstrated reduction in heart failure (HF) hospitalization regardless of the presence or absence of diabetes.[3,68] Consideration should be given to either stopping or dose-reducing other hypoglycemic agents in order to accommodate SGLT2i therapy.[51] Finally, metformin is recommended for patients with HFpEF and DM with an eGFR greater than 30 mL/min/1.73 m^2 given associated mortality benefits.[70]

Up to 80% of patients with HFpEF are either overweight or have obesity.[51] Compared with nonobese HFpEF patients, these patients were noted to have significantly greater right ventricular dilation and concentric LV remodeling, increased epicardial fat thickness, and greater total epicardial heart volume.[71,72] Weight loss was shown to have beneficial effects for these patients, with caloric restriction and aerobic exercise training associated with increased peak oxygen consumption and markers of inflammation.[18] Bariatric surgery is associated with the most dramatic and sustained weight loss; however, only one small, noncontrolled study for patients with mild HFpEF showed improvements in symptom severity.[73] The glucagon-like peptide-1 (GLP-1) receptor antagonist medication class is a novel pharmacologic weight loss therapy with increasing implications for exercise augmentation, as discussed later.

Pharmacologic Treatments

Although historically medical therapeutics for patients with HFpEF have struggled to demonstrate significant benefits, recent trial data have introduced new pharmacologic interventions that not only improve functional capacity but are shown to positively impact morbidity and mortality for patients with HFpEF.[49,51] Indeed, LVEF cut-off values have ranged widely in clinical trials for HFpEF from as low as 35% to greater than 55% and are acknowledged in the ACC/AHA/HFSA heart failure guidelines, impacting interpretation of epidemiologic data and clinical outcomes.[3,74]

Promising trials regarding therapeutic management for HFpEF were demonstrated in 2021 and 2022 with the EMPEROR-Preserved and Deliver trials, respectively.[75] In the EMPEROR-Preserved trial, patients assigned to empagliflozin experienced a 21% reduction in the primary composite outcome of HF hospitalizations or cardiovascular mortality (hazard ratio [HR]: 0.79 [95% confidence interval [CI]: 0.69–0.90], *P*<.001). These findings were appreciated across subgroups defined by diabetes, LVEF, and background medical therapy.[68] The DELIVER trial demonstrated that patients assigned to dapagliflozin experienced an 18% reduction in the primary composite outcome of worsening HF or cardiovascular death (HR 0.82 [95% CI, 0.73–0.92], *P*<.001). These findings were also demonstrated across subgroups, including those defined by diabetes and LVEF.[76] Given the beneficial outcomes found in recent clinical trials, the 2022 ACC/AHA guidelines now recommend SGLT2i therapy to be initiated in all individuals with HFpEF lacking contraindications (Class IIa recommendation).[3] Key contraindications to SGLT2i therapy include Type 1 DM, a history of DKA, and an eGFR less than 20 mL/min/1.73 m^2. Additionally, the EMPULSE trial evaluated the effect of empagliflozin versus placebo in patients with acutely decompensated HF and noted more rapid decongestion and significant improvement in secondary composite endpoint including health status and clinical outcomes across LVEF.[77] This data reaffirm SGLT2i therapy as a valuable regimen for HFpEF and supports predischarge initiation of these therapies.

Mineralocorticoid antagonists, including ARBs, ARNIs, and mineralocorticoid receptor antagonists (MRAs), are additional agents that can be considered for specific subgroups within the HFpEF population (Class IIb recommendation).[3]

The role of ARNI in management of HFpEF was evaluated in the PARAGON-HF trial, which showed a numerically decreased primary composite endpoint of HF hospitalizations and cardiovascular death between sacubitril valsartan (97/103 mg twice daily) and valsartan (target dose 160 mg daily); however, the results were not statistically significant (HR 0.87 [95% CI, 0.75–1.01], *P*=.06).[67] Post hoc analyses, however, suggested patients enrolled within 30 days of hospitalization showed significantly greater risk reduction for the primary composite endpoint.[78] Additionally, subgroup analyses, suggested potential benefit in patients with LVEF between 45% and 57% (HR 0.78 [95% CI, 0.64–0.95]) and in women compared with men (HR 0.78 [95% CI, 0.59–0.90]).[79] Given these findings, ARNI initiation for HFpEF is recommended for women regardless of LVEF and men with LVEF less than 55% to 60% (Class IIb recommendation).[3,51]

MRAs were first evaluated for effects on clinical outcomes in the management of HFpEF in the TOPCAT trial. Although initial results did not show a significant benefit (HR 0.89 [95% CI, 0.77–1.04]),[80] a subgroup analysis of patients within North America found a significant reduction in the primary composite endpoint (HR 0.82 [95% CI, 0.69–0.98]).[81] As a result, guidelines provide a Class IIb recommendation for MRAs to reduce hospitalizations, especially in patients with EF less than 55% to 60%.[3,51] Recently, the FINEARTS-HF trial tested the efficacy of finerenone, a nonsteroidal MRA, in patients with HFmrEF and HFpEF. This trial demonstrated that finerenone as compared with placebo resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes (RR 0.84 [95% CI, 0.71–0.95], P=.007).[82] Additionally, secondary outcomes noted finerenone to improve patient-reported symptoms compared with placebo, as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score at 12 months (8.0 ± 0.3 points vs 6.4 ± 0.3 points; difference, 1.6 points; [95% CI, 0.8–2.3], P<.001). Recommendations addressing the guideline-directed management of HFmrEF and HFpEF have not been updated at the time of this publication to reflect these potential benefits for finerenone.[3]

Lastly, the GLP-1 agonist reflects an area of increasing focus in current trials. The SUMMIT trial evaluated the efficacy and safety of tirzepatide compared with placebo in patients with HFpEF and obesity. The trial found tirzepatide to have a lower composite of adjudicated death from cardiovascular causes or worsening heart failure (HR 0.62 [95% CI, 0.41–0.95], P=.026). Additionally, the trial noted a mean improvement in KCCQ clinical summary scores (19.5 ± 1.2 points vs 12.7 ± 1.3 points; difference 6.9 points; [95% CI, 3.3–10.6], P<.001).[83] Furthermore, a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM trials demonstrated semaglutide significantly reducing the risk of the composite endpoint of cardiovascular death or first worsening heart failure event compared with placebo (5.4% vs 7.5%, HR 0.69 [95% CI, 0.53–0.89], P=.0045) along with a reduction in worsening heart failure events alone (2.8% vs 4.7%, HR 0.59 [95% CI 0.41–0.82], P=.0019).[84] GLP-1 agonists have also demonstrated efficacy in reducing HF hospitalizations and improving renal outcomes for patients with HFpEF.[85] When used alongside SGLT2i, these agents are shown to provide summative cardiorenal protection, particularly beneficial for patients with type 2 diabetes and CKD.[86] Finally, GLP-1 agonists are also increasingly utilized as interventions for weight loss for patients with HFpEF and obesity along with bariatric surgery. However, although bariatric surgery can achieve weight loss, it tends to increase NT-proBNP levels postoperatively. GLP-1 agonists, on the other hand, have been shown to significantly reduce NT-proBNP levels, promoting hemodynamic benefits and improving physical mobility.[87] Although current heart failure guidelines do not yet include the use of GLP-1 agonists as part of guideline-directed medical therapy (GDMT),[3] the gathering evidence suggests future inclusion for patients with HFpEF and obesity[51] (**Table 2**).

These recommendations differ slightly for patients with HFmrEF with an LVEF 41% to 49% or heart failure with improved ejection fraction (HFimpEF). For HFmrEF patients, SGLT2i remains a Class IIa recommendation. Additionally, evidence-based beta-blockers have a Class IIb recommendation along with ARNI/ACEi/ARBs and MRAs, and these pharmacotherapies are preferred for patients with an LVEF on the lower end of the HFmrEF spectrum.[3] For HFimpEF patients, GDMT for HFrEF carries a Class I recommendation for maintenance therapy.[3,88]

Table 2
Guideline-directed medical therapy for heart failure with preserved ejection fraction

Medication	Indications	Class of Recommendation
Diuretics	Prevent congestion if fluid retention or NYHA Class III and IV	Class I
SGLT2i	First-line for all patients with HFpEF	Class IIa
ARNI/ARB/MRA	Add-on therapy, favor if LVEF < 55%–60%	Class IIb
GLP-1 RA	Potential benefit particularly in patients who are overweight or obese to manage T2DM and promote weight loss	No recommendation
Beta-blockers	May be considered in patients with specific indications (eg prior myocardial infarction, angina, or AF) but should generally be avoided due to potential negative chronotropic effects	No recommendation

Nonpharmacologic Interventions

Exercise interventions have consistently demonstrated large, significant, and clinically meaningful improvements in HF symptoms for patients with HFpEF, with a comparable or even larger magnitude of improvement compared with patients with HFrEF.[89] As a result, exercise training is recommended for improvement of functional status, exercise performance, and quality of life per ACC/AHA guidelines (Class I recommendation).[3] Enrollment of HFpEF patients in outpatient cardiac rehabilitation after hospitalization was associated with significantly lower risk of all-cause mortality and HF rehospitalization, emphasizing its viability as an effective management strategy for these patients.[90]

FUTURE DIRECTIONS

Remote Pulmonary Artery Pressure Monitoring

Remote monitoring of PA pressures has emerged as an effective strategy to reduce heart failure hospitalizations in patients with New York Heart Association (NYHA) Class III symptoms.[91,92] Monitoring of PA pressures serves as a surrogate for measuring preload, allowing patients to transmit this data from home to their providers in order to have their medication regimen for heart failure adjusted remotely in the outpatient setting. Clinical trials validating the use of remote PA pressure monitoring have included heart failure patients across all ranges of EF including those with HFpEF. A subgroup analyses of HFpEF patients have shown variable efficacy in reducing heart failure hospitalizations in this group.[25,93] Indeed, the GUIDE-HF trial evaluated the role of PA pressure-guided heart failure management using the CardioMEMS HF System. The trial noted no significant difference in the composite outcome of all-cause mortality and total heart failure events at 12 months (HR 0.88, [95% CI 0.74–1.05], *P*=.16). However, in a prespecified COVID-19 sensitivity analysis, there was a significant reduction in HF events in the PA pressure-guided group (HR 0.81, [95% CI 0.66–1.00], *P*=.049).[94] Considering these findings, the use of implantable devices to monitor pulmonary arterial pressures is a suggested strategy to limit frequency of hospitalizations, particularly for patients with vague or labile volume states (Class IIb recommendation).[3,51] These initial systems used to monitor PA pressures remotely transmitted measurements while patients were supine. This was thought to be a barrier to adherence, as patients may be reluctant to lay flat due to symptoms of orthopnea. Recently the Food and Drug Adminstration-approved Cordelia PA Sensor and HF system was developed allowing patients to transmit PA pressure measurements while seated. Early analysis of enrolled patients 6 months into the PROACTIVE-HF trial has demonstrated a lower incidence of HF hospitalizations as compared with prior trials with supine monitoring, and the results are consistent in a subgroup analysis of patients with HFpEF.[95]

Splanchnic Nerve Ablation

The splanchnic circulation is thought to be a high-capacitance vascular system capable of holding large amounts of blood volume with significant resultant shifts in hemodynamics. Activation of the splanchnic nervous system is thought to cause vasoconstriction, leading to shifting of blood volume from the peripheral to the central circulation. In HFpEF, it has been shown that inhibition of the splanchnic nerve may result in splanchnic vasodilation with resultant shifting of blood volume out of the central circulation leading to decreases in congestion and intracardiac pressures.[96,97] More recently and specifically in HFpEF patients, the REBALANCE-HF randomized clinical trial showed that an endovascular approach to permanent denervation of the right splanchnic nerve was associated with safe outcomes at 1-year postintervention.[98] However, there was no statistically significant difference in leg-raise or exercise PCWP at 1 month between the treatment and sham control group, nor was there a statistically significant difference in HF hospitalizations or exercise capacity at 12 months between the 2 groups.

Cardiac Contractility Modulation

Cardiac contractility modulation (CCM) is a device that delivers a nonexcitatory shock during the absolute refractory phase of the cardiac cycle, ultimately resulting in increased contractility, reverse remodeling of the LV, and improved EF in HFrEF patients.[99] CCM has also been shown in animal models of HFrEF to improve the expression of titin, the protein responsible for myocyte relaxation, rendering it a potential target for HFpEF therapy.[100] A study looking at 47 HFpEF patients over 24 weeks after CCM implantation showed a significant improvement in KCCQ score, a subjective self-assessment of functional status and symptomatology in heart failure.[101] A subsequent analysis revealed a reduction in the number of patients experiencing heart failure hospitalizations within the year after CCM implantation as compared with the year prior.

Frailty and Sarcopenia

Frailty and sarcopenia often coexist with heart failure and are associated with worse outcomes including all-cause mortality and hospitalizations in heart failure patients.[102,103] As such, it is important to assess for frailty in heart failure patients. Currently, there is no standardized frailty assessment tool specific to heart failure, but 2 widely accepted comprehensive assessment tools are the Fried Phenotype Model and the frailty index tool. Additionally, grip strength and gait speed can be used as markers of frailty on their own or as part of the aforementioned testing. With regards to intervention, the REHAB-HF trial explored initiating a rehabilitation program to enhance balance, mobility, strength, and endurance while elderly patients were inpatient and continued for 36 sessions in the outpatient setting. The intervention group did score higher on the Short Physical Performance Battery, a standardized measure of global physical function, without an appreciable difference in rehospitalization after 6 months or mortality.[104] From a nutritional standpoint, PICNIC was an RTC in patients hospitalized with acute decompensated heart failure (ADHF) where patients in the intervention group received 6 months of nutritional counseling (diet optimization, specific recommendations, and nutritional supplementation). Patients in the treatment group had both reduced HF readmission and mortality.[105] While more studies are needed to assess the impact of frailty interventions in heart failure, physicians should be addressing frailty and sarcopenia with the current available resources.

SUMMARY

Given its growing prevalence and improving treatability and diagnostic tools, it is important that health care practitioners from generalists to subspecialists develop a high clinical index of suspicion for HFpEF in certain patients and comfortable approach to its diagnosis. Many HFpEF patients may not have classic signs of heart failure such as elevated BNP/NTProBNP, overt congestion, or elevated filling pressures at rest; it is important to utilize probability tools such as H2FPEF and HFA-PEFF to aid in diagnosis. Although the gold standard test for HFpEF is invasive hemodynamic exercise testing, other methods such as stress TTE, PLR, and fluid challenge can be pursued if supine exercise with RHC is not available. Management of HFpEF has evolved over the years and currently strongly relies on diuresis and management of comorbidities such as HTN, CAD, AF, CKD, DM, frailty, and obesity. SGLT2i and MRAs have emerged as Class IIa and IIb treatment recommendations, respectively. Excluding other HF mimickers is important when evaluating for HFpEF, as many clinical conditions masquerading as heart failure have different and more targeted therapies. Seated remote PA pressure monitoring and cardiac contractility modulation are promising emerging management options for HFpEF.

CLINICS CARE POINTS

- Approximately 50% of patients with heart failure have preserved ejection fraction, and HFpEF confers a similar risk of morbidity and mortality as HFrEF.
- Prior to widespread adoption of the term HFpEF, "diastolic heart failure" was often used to denote this syndrome; the substitution of this term for HFpEF is no longer recommended.
- The diagnosis of HFpEF may be challenging in some patients due to other conditions masquerading as heart failure; standard evaluation should include a workup for noncardiac causes of symptoms with the aid of diagnostic algorithms and specialized testing when indicated.
- Management of HFpEF emphasizes relief of congestion, treatment of comorobidities, and use of SGLT2 inhibitors, ARNI and MRA as guideline-directed medical therapies with specific albeit less robust evidence in this subgroup of heart failure patients.

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